

REMARKS

Applicants have added new claim 74. Support for this amendment can be found throughout the specification as filed, for example, at page 20, lines 21-23.

35 U.S.C. § 103(a) – Obviousness

The Examiner rejects all pending claims under 35 U.S.C. § 103(a) as obvious over Shoshan (WO0210449) in view of Bennett (US 6172216) and Wengel for the reasons of record. The Examiner previously asserted that Shoshan discloses a 65 base oligonucleotide, SEQ ID NO: 28624, which “is disclosed as an RNA transcript or splice variant of a transcript (see ¶[0115]),” and to which “SEQ ID NO:19 of the instant invention is 100% complementary.” *Previous Office Action* at 3. The Examiner also asserts that Shoshan “teach that these RNA transcripts can be used as the basis for designing antisense RNA and siRNA. (see ¶ [0111] through [0113]).” *Id.* The Examiner asserted that it would be obvious to make antisense to SEQ ID NO: 28624 based on Shoshan, and that the modifications and pharmaceutical compositions recited in the claims are obvious in view of Bennett and Wengel. Applicants respectfully traverse.

In Applicants’ previous response, Applicants argued that Shoshan offers no reason to select SEQ ID NO: 28624 for designing antisense, and that the Examiner has failed to provide any reason why it is obvious to select this particular sequence out of the 32,337 sequences disclosed, or to select the antisense oligonucleotides of the pending claims out of the literally tens of millions of potential antisense that could be designed based on Shoshan.

The Examiner responds by arguing that there is no reason Shoshan’s teaching of antisense based upon the oligonucleotides of the present invention “would not be readily applicable to an explicitly described species of the oligonucleotides of Shoshan et al., namely SEQ ID NO: 28624.” *Office Action* at 3. The Examiner concludes that “the ordinary skilled artisan reading the Shoshan et al. reference would have a reasonable expectation ... that this generic reference [to antisense] would also apply to the specifically disclosed species of oligonucleotide disclosed in this reference.” *Id.*

Applicants agree that Shoshan’s general statement is applicable to all of the “oligonucleotides of the invention,” and therefore one of skill could design an antisense sequence of any of the 32,337 explicitly described species of the oligonucleotides of Shoshan. However,

this begs the question of why one of skill in the art would select SEQ ID NO: 28624 out of the 32,337 potential sequences.

The Examiner continues, explaining how the Shoshan reference was discovered:

The Shoshan reference was identified by means of searching SEQ ID NO: 19 of the instant invention, wherein SEQ ID NO: 28624 was identified as fully encompassing SEQ ID NO: 19. The only difference between the prior art sequence and the compound of claim 1, was a difference of 15 base pairs. It was not the generic disclosure of the oligonucleotides of Shoshan et al. that identified this reference as potential prior art, it was the specifically disclosed sequence of SEQ ID NO: 28624. Furthermore, the disclosure of Shoshan et al. explicitly provides motivation to use all of the specifically disclosed sequences as potential templates for designing antisense and/or siRNA compounds. *Office Action* at 3-4 (emphasis added).

Applicants submit that the Examiner is engaging in impermissible hindsight analysis. While Applicants recognize the need to use the claimed invention to find the closest related art, once the reference is located, it must be analyzed to determine what one of skill in the art would have understood the reference to teach at the time of the invention without the benefit of Applicants' disclosure to guide the analysis – to do otherwise is to impermissibly use hindsight. When Shoshan is viewed without the benefit of Applicants' disclosure of SEQ ID NO: 19 or claimed compounds, one of skill in the art is faced with the disclosure of 32,337 “potential templates for designing antisense,” to use the Examiner’s own language. *Office Action* at 4. Thus, the Examiner must argue that one of skill in the art would select SEQ ID NO: 28624 out of 32,337 “potential templates,” and make antisense to that sequence in the absence of Applicants' disclosure. Clearly, without Applicants' disclosure there is no reason to select SEQ ID NO: 28624.

Perhaps in recognition of the fact that there is no reason to select SEQ ID NO: 28624, the Examiner argues that one of skill in the art “would have been motivated to design the compounds of the instant invention, since the target sequence of Shoshan et al. is explicitly disclosed.” *Office Action* at 5 (emphasis added). The Examiner is arguing that explicit disclosure of a sequence, regardless of the number of other sequences that are also disclosed, is sufficient to provide a motivation to make antisense to the sequence and thus establish *prima facie* obviousness. This is an unreasonable position that is contrary to controlling caselaw from the Federal Circuit.

In *Takeda Chem. Indust., Ltd. v. Alphapharm Pty., Ltd.*, defendant Alphapharm argued that the claimed compound was obvious over a reference that expressly disclosed numerous compounds of the claimed class of compounds, including a specifically disclosed homolog of the claimed compounds referred to as "compound b." *Takeda Chem. Indust., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). Alphapharm asserted that the prior art provided a reason to select "compound b" as a starting point for making modifications to discover a superior compound, and that using "compound b" as the starting point, one of skill in the art would have arrived at the claimed compound by making obvious modifications. *Id.* Relying on *KSR*, Alphapharm argued that modification of "compound b" would have been "obvious to try" given its disclosure and a reason in the art to select compound b as the starting point for modification. *Id.* at 1359.

The Federal Circuit affirmed the district court's rejection of Alphapharm's arguments. The court held that the district court did not err in finding that Alphapharm failed to establish that there was a basis to select "compound b" as the starting compound for further modification out of all of the disclosed compounds. In the absence of any reason to select "compound b," the Federal Circuit affirmed the lower court's decision that the claimed compounds were not obvious. In doing so, the court specifically rejected Alphapharm's reliance on *KSR* stating:

The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. *Id.* at 1359 (emphasis added).

Applicants submit that *Takeda* is directly applicable to the instant case. Like *Takeda*, the Shoshan reference discloses thousands of starting points for one of skill in the art to investigate new compounds, "any one of which could have been selected" for further investigation. The Examiner's obviousness argument, like Alphapharm's, requires that a single starting compound, SEQ ID NO: 28624, be selected from the long list of disclosed compounds. As was the case in *Takeda*, the starting compound is expressly disclosed in the cited reference. However, unlike Alphapharm, the Examiner has not even attempted to provide a reason one of skill in the art

would select the particular starting compound, instead merely relying on the fact that it is expressly disclosed.

The *Takeda* court implicitly held that express disclosure of the starting compound was not sufficient for obviousness – a reason to select the starting compound and make modifications was required. Were mere disclosure of the starting compound sufficient, the court would have ignored Alphapharm's arguments about why "compound b" was the preferred starting material, and upheld the obviousness rejection merely because "compound b" was disclosed. Thus, the Examiner cannot simply rely on the fact that SEQ ID NO: 28624 is expressed – there must be a reason to select it from the 32,336 other sequences.

In addition, the court specifically addressed *KSR* and found that it did not alter the court's analysis: "We do not accept Alphapharm's assertion that *KSR*... mandates reversal." *Id.* at 1359. Thus, the court has implicitly rejected the Examiner's argument based on *KSR* that the claimed compounds are obvious because all of the claimed elements were known in the prior art and one of skill in the art could have combined the elements as claimed by known methods to yield predictable results. *Office Action* at 6.

Finally, Applicants address the Examiner's argument that Applicants are impermissibly attacking each of the references individually. *Office Action* at 4. As stated above, controlling caselaw requires that the Examiner provide some reason to select SEQ ID NO: 28624 as a starting material. The Examiner has not relied on either of Bennett or Wengel to provide this rationale, instead relying solely on Shoshan's disclosure of SEQ ID NO: 28624. For the reasons discussed above, Shoshan does not provide the required rationale. Neither of Bennett or Wengel overcome this shortcoming, alone or in combination, as the Examiner has not pointed to any portion of either reference which would provide a basis for the selection of SEQ ID NO: 28624.

In sum, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because there is no basis to select SEQ ID NO: 28624 from the 32,337 disclosed sequences in Shoshan. As the court in *Takeda* makes clear, mere disclosure of the starting compound is not sufficient. In view of the "broad selection of compounds any one of which could have been selected as a lead compound for further investigation," there must be some reason to select a particular compound. *Takeda* at 1359. For at least the above reasons,

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Applicants request reconsideration and withdrawal of the rejection of the pending claims as obvious over Shoshan in view of Bennett and Wengel.

Unexpected Results Must Be Considered

Finally, even if the Examiner has established a *prima facie* case of obviousness, a point which Applicants do not concede, Applicants submit that compounds of the currently pending claims have unexpected properties which are more than sufficient to overcome any *prima facie* case of obviousness that the Examiner has presented. "The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983) that 'evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness.'" *M.P.E.P.* §716.01(a) (emphasis added). The Examiner has not yet addressed Applicants' arguments of unexpected results, and Applicants respectfully request consideration of the following evidence.

In particular, Applicants note that in Example 15, Table 1, of the instant specification, SEQ ID NO: 19 shows 79% inhibition of Human Growth Hormone Receptor expression *in vitro*. This result is clearly unexpected in view of the cited references which do not disclose any information regarding SEQ ID NO: 28624, including whether SEQ ID NO: 28624 represents a portion of the transcript accessible to antisense molecules *in vitro*. There is simply no basis in the art to expect that SEQ ID NO: 19 would have such a high level of inhibitory activity. Given that any *prima facie* case of obviousness is extremely weak, this unexpected property is more than sufficient to overcome it.

For at least this additional reason, Applicants request reconsideration and withdrawal of the rejection of the pending claims as obvious over Shoshan in view of Bennett and Wengel.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other

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broad or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents/Applications

Applicants wish to draw the Examiner's attention to the following patents/applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents/applications throughout the pendency of this application.

Serial Number	Title	Filed
10/927,466	MODULATION OF GROWTH HORMONE RECEPTOR EXPRESSION AND INSULIN-LIKE GROWTH FACTOR EXPRESSION	08/25/2004
10/547,239	MODULATION OF GROWTH HORMONE RECEPTOR EXPRESSION AND INSULIN-LIKE GROWTH FACTOR EXPRESSION	08/25/2005

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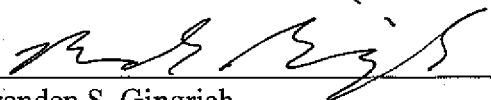
CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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